Hypoglycemics, SGLT2 Inhibitors

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indications
canagliflozin (Invokana®)[1]	Janssen	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
canagliflozin / metformin (Invokamet®)[2]	Janssen	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing metformin or canagliflozin or in patients already being treated with both canagliflozin and metformin
dapagliflozin (Farxiga®)[3]	AstraZeneca	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
dapagliflozin / metformin ER (Xigduo®)[4]	AstraZeneca	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate
empagliflozin (Jardiance)[5]	Boehringer Ingelheim	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Agents in this review are not indicated for the treatment of type 1 diabetes or diabetic ketoacidosis.

OVERVIEW

It is estimated that 29.1 million people in the U.S. have diabetes.[6] Type 2 diabetes accounts for about 90 to 95 percent of all diagnosed cases of diabetes in adults. Improved glycemic control benefits patients with either type 1 or type 2 diabetes. In general, for every one percent reduction in hemoglobin A1c (HbA1c), the risk of developing microvascular diabetic complications (eye, kidney, and nerve disease) is reduced by 40 percent.[7]

In addition to exogenous insulin, there are several pathways by which blood glucose is regulated in diabetic patients. The sodium-glucose cotransporter (SGLT2) inhibitors reduce renal glucose reabsorption in the proximal convoluted tubule, leading to increased urinary glucose excretion. There have been no clinical studies that have established conclusive evidence of macrovascular risk reduction with the SGLT2 inhibitors.

In 2015, the American Diabetes Association (ADA) Standards of Medical Care in Diabetes were updated and included the sodium-glucose cotransporter-2 (SGLT2) inhibitors in the management algorithm for type 2 diabetes.[8] The position statement recommends HbA1c of less than seven percent as a reasonable target for most nonpregnant patients. Metformin is recommended for the treatment of type 2 diabetes, along with lifestyle interventions at the time of diagnosis, unless metformin is contraindicated.[9] If metformin fails to produce the target HbA1c after three months of therapy, either a TZD, sulfonylurea, DPP-4 inhibitor, SGLT-2 inhibitor, GLP-1 receptor agonist, or insulin should be added. In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or A1C, insulin therapy should be considered, with or without additional agents. If target HbA1c is still not achieved after an additional three months, then an agent from a different group listed should be added. Therapy should be individualized based on the needs, preferences, and tolerances of each patient. Patients with type 2 diabetes are at increased risk of cardiovascular morbidity and mortality; therefore, aggressive management of cardiovascular risk factors (e.g., blood pressure and lipid therapy, antiplatelet treatment, and smoking cessation) should be part of multifactorial risk reduction approach.[10]

The American Association of Clinical Endocrinologists (AACE) established new guidelines in 2013 for glycemic control.[11] The 2013 AACE treatment algorithm stratifies choice of therapy based on the patient's initial HbA_1C level: less than 7.5 percent, ≥7.5 percent, and greater than nine percent. The guidelines suggest patients with an HbA1c level less than 7.5 percent start with monotherapy, whereas patients with an HbA1c level ≥7.5 percent begin with dual therapy. Patients with an HbA1c greater than nine percent and no symptoms may start on either dual or triple antihyperglycemic therapy; patients with an HbA1c greater than nine percent with symptoms should begin insulin therapy, with or without other agents. The patient's HbA_1C should be reassessed every three months and failure to improve may warrant additional complementary therapy for optimal glycemic control. Within each therapy group (monotherapy, dual therapy, and triple therapy), the guidelines provide a hierarchical order of the usage of drugs where, like the ADA guidelines, metformin is the preferred treatment of choice for monotherapy and first-line agent for dual and triple therapy. The AACE guidelines suggest SGLT2 inhibitors as a fifth, fourth, and third choice in monotherapy, dual therapy, and triple therapy, respectively. AACE advises using SGLT2 inhibitors with caution and acknowledges that their place in therapy for diabetes management remains undefined due to lack of experience with these agents. The SGLT2 drugs will likely be used as add-on therapy to two or three other agents, including insulin, in patients who would benefit from weight loss.

The product empagliflozin/linagliptin (Glyxambi®), which combines an SGLT2 inhibitor and a dipeptidyl peptidase-4 (DPP-4) inhibitor, is not included in this clinical review.

PHARMACOLOGY [12,13,14,15,16]

Canagliflozin (Invokana, Invokamet), dapagliflozin (Farxiga, Xigduo XR), and empagliflozin (Jardiance) are sodium-glucose cotransporter 2 (SGLT2) inhibitors. SGLT2, which is expressed in the proximal renal tubules, is the transporter responsible for the majority of the reabsorption of filtered glucose from the tubular lumen in the kidney. By inhibiting SGLT2, these agents reduce reabsorption of filtered glucose and lower the renal threshold for glucose (RTG), thereby increasing urinary glucose excretion and improving blood glucose control.

Metformin (Invokamet, Xigduo XR), a biguanide, decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

PHARMACOKINETICS [17,18,19,20,21]

Drug	Bioavailability (%)	Tmax (hr)	Half-life (hr)	Metabolism	Excretion (%)
canagliflozin (Invokana)	65	1-2	10.6 - 13.1	hepatic (O-glucuronidation via UGT1A9 & 2B4; 2 inactive metabolites)	feces: 60 urine: 33
dapagliflozin (Farxiga)	78	<2	12.9	hepatic (UGT1A9; 1 inactive metabolite)	feces: 21 urine: 75
empagliflozin (Jardiance)	nr	1.5	12.4	hepatic (O-glucuronidation via UGT1A3 & 1A8, & 1A9)	feces: 41.2 urine: 54.4
metformin	50-60	nr	6.2	no metabolites have been identified in humans	feces: nr urine: 90

The bioequivalence of canagliflozin/metformin (Invokamet) and dapagliflozin/metformin ER (Xigduo XR) combinations are bioequivalent to co-administration of corresponding doses of their individual components under fed conditions.

CONTRAINDICATIONS/WARNINGS [22,23,24,25,26]

Canagliflozin (Invokana, Invokamet), dapagliflozin (Farxiga, Xigduo XR), and empagliflozin (Jardiance) are contraindicated in patients with a history of serious hypersensitivity reactions to the active ingredient. The single component SLGT2 inhibitors are contraindicated in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] less than 30 mL/min/1.73 m^2), end stage renal disease (ESRD), and in patients on dialysis; the combination product, canagliflozin/metformin (Invokamet), is contraindicated in patients with eGFR less than 45 mL/min/1.73 m^2; the combination dapagliflozin/metformin ER (Xigduo) is contraindicated in patients with serum creatinine level of 1.5 mg/dL or greater in men and 1.4 mg/dL or greater in women, or eGFR less than 60 ml/min/1.73 m^2 or CrCL less than 60 mL/min.

Hypersensitivity reactions have occurred when using canagliflozin. If hypersensitivity reactions occur, canagliflozin should be discontinued and the patient should be treated per standards of care and monitored until signs and symptoms resolve.

Metformin-containing products (Invokamet, Xigduo XR) are contraindicated in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis. The label carries a boxed warning that, although rare, potentially fatal lactic acidosis can occur due to metformin therapy. This risk increases with renal or hepatic impairment, sepsis, dehydration, excessive alcohol intake, and acute congestive heart failure.

Combination agents containing metformin (Invokamet, Xigduo XR) carry boxed warning regarding the risk of lactic acidosis which can occur with metformin accumulation. The risk increases with sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure. Treatment including metformin should be discontinued and the patient hospitalized immediately if lactic acidosis is suspected.

Symptomatic hypotension can occur after starting SGLT2 inhibitors as they cause osmotic diuresis leading to intravascular volume contraction. Symptomatic hypotension occurs particularly in patients with impaired renal function (estimated glomerular filtration rate [eGFR] less than 60 mL/min/1.73 m^2), elderly patients, patients with low systolic blood pressure, and patients on diuretics or drugs which interfere with the renin-angiotensin-aldosterone system. The patient's volume status should be assessed and corrected prior to starting SGLT2 inhibitor therapy and monitored thereafter.

SGLT2 inhibitors can decrease the eGFR and increase serum creatinine. Patients with hypovolemia, particularly the elderly and those with moderate renal impairment, may be at an increased risk for these changes. Renal function should be evaluated prior to initiation and monitored periodically thereafter.

Canagliflozin can cause hyperkalemia. Patients with moderate renal impairment who are also taking medications that interfere with potassium excretion or the renin-angiotensin-aldosterone system are more susceptible to the development of hyperkalemia. Potassium levels should be monitored regularly after beginning canagliflozin in patients with impaired renal function and in patients who are predisposed to increased potassium levels due to mediations or other medical conditions.

SGLT2 inhibitors can increase the risk of hypoglycemia when combined with insulin or insulin secretagogues; therefore, a lower dose of insulin or insulin secretagogue may be required when given in combination with a SGLT2 inhibitor.

Patients with a history of genital mycotic infections and uncircumcised males are more likely to develop mycotic infections when using SGLT2 inhibitors and should be monitored closely. Patients treated with SGLT2 inhibitors are also at increased risk for urinary tract infections and should be monitored closely.

SGLT2 inhibitors may cause dose-related increases in low-density-lipoprotein cholesterol (LDL-C); therefore, monitoring is warranted to determine the need for treatment intervention.

The incidence of bladder cancer reported in clinical trials was 0.17 percent in patients treated with dapagliflozin (Farxiga, Xigduo XR) compared with a 0.03 percent incidence in the placebo arm. Bladder cancer risk factors were equally balanced between the two groups at baseline. After excluding patients who had less than a one-year exposure to dapagliflozin at time of bladder cancer diagnosis, there were four cases in the dapagliflozin arms and no cases in the placebo arms of these trials. At this time, there is insufficient data to determine whether dapagliflozin has an effect on pre-existing bladder tumors. Dapagliflozin should not be used in patients with active bladder cancer or a prior history of bladder cancer. To date increased risk of bladder cancer has not been reported with products containing canagliflozin (Invokamet, Invokana) or empagliflozin (Jardiance).

Temporarily discontinue canagliflozin/metformin and dapagliflozin/metformin in patients undergoing radiologic procedures who receive intravenous iodinated contrast agents and in patients undergoing any surgical procedure associated with restricted intake of food and fluids. Caution should be used with metformin-containing products in patients experiencing hypoxic states.

DRUG INTERACTIONS [27,28,29,30,31]

When administered with UDP-Glucuronosyl Transferase (UGT) enzyme inducers (e.g., rifampin, phenytoin, ritonavir, phenobarbital), the exposure of canagliflozin (Invokana, Invokamet) is reduced, which may decrease the efficacy of canagliflozin. If co-administration is needed and the patient has an eGFR greater than 60 mL/min/1.73 m^2, prescribers should consider increasing the dose from 100 mg to 300 mg once daily, if tolerated. Other antihyperglycemic therapy should be considered in patients with an eGFR of 45 to 59 mL/min/1.73 m^2 who are also taking an UGT inducer and require additional glycemic control. Empagliflozin (Jardiance) does not inhibit UGT1A1; therefore, no drug interaction is expected when co-administered with substrates of this enzyme. Although metabolism of dapagliflozin (Farxiga, Xigduo XR) involves UGT enzymes, current labeling does not report drug interactions with concurrent use of UGT enzyme inducers.

Co-administration of digoxin and canagliflozin 300 mg may increase the exposure to digoxin and, therefore, close monitoring is warranted.

Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter, and the dapagliflozin 3-0-glucoronide metabolite is a substrate for the OAT3 active transporter. Dapagliflozin has not been shown to induce nor inhibit any of the cytochrome isoenzymes or P-gp, OCT2, OAT1, or OAT3 active transporters. None of the co-administered drugs that were studied (including other classes of oral antidiabetic medications or rifampin) have demonstrated the need for dosage adjustment when given concomitantly with dapagliflozin. Empagliflozin is a substrate for uptake transporters P-gp, OAT3,

OATP1B1, and OATP1B3, but does not inhibit these transporters at clinically relevant plasma concentrations; therefore, no relevant drug interactions are expected.

Cationic drugs, such as amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin, that are eliminated by renal tubular secretion have a theoretical potential interaction with metformin by competing for common renal tubular transport systems. No specific dosing changes are recommended. Increased metformin plasma concentrations are seen with concurrent administration of cimetidine, furosemide, and nifedipine. No specific dosing changes are recommended. Contrast agents increase the risk of metformin-induced lactic acidosis. Concomitant use of topiramate or other carbonic anhydrase inhibitors may increase the risk of lactic acidosis. Monitor for signs and symptoms of acidosis when these drugs are used concomitantly with metformin-containing agents (Invokamet, Xigduo XR).

ADVERSE EFFECTS [32,33,34,35,36]

Drug	genital mycosis, female	Urinary Tract Infection	Increased Urination	genital mycosis , male	Vulvovaginal pruritus	Thirst	Constipation	Nausea	Nasopharyngitis	Back Pain	Influenza	Dyslipidemia	Discomfort with urination	Pain in extremity
canagliflozin (Invokana)	10.4-11.4 (3.2)	4.3-5.9 (4)	4.6-5.3 (0.8)	3.7-4.2 (0.6)	1.6-3 (0)	2.3-2.8 (0.2)	1.8-2.3 (0.9)	2.2-2.3 (1.5)	nr	nr	nr	nr	nr	nr
dapagliflozin (Farxiga)	6.9-8.4 (1.5)	4.3-5.7 (3.7)	2.9-3.8 (1.7)	2.7-2.8 (0.3)	nr	nr	1.9-2.2 (1.5)	2.5-2.8 (2.4)	6.3-6.6 (6.2)	3.1-4.2 (3.2)	2.3-2.7 (2.3)	2.1-2.5 (1.5)	1.6 - 2.1 (0.7)	1.7-2 (1.4)
empagliflozin (Jardiance)	5.4-6.4 (1.5)	7.6-9.3 (7.6)	3.2-3.4 (1)	1.6-3.1 (0.4)	nr	1.5-1.7 (0)	nr	1.1-2.3 (1.4)	nr	reported	nr	2.9-3.9 (3.4)	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

When used alone, SGLT2 inhibitors do not appear to cause hypoglycemia. SGLT2 inhibitors result in modest weight loss.

As communicated by the FDA, urine glucose tests should not be used to monitor glycemic control in patients that are on SGLT2 inhibitors.[37] SGLT2 inhibitors increase urinary glucose excretion and will result in positive urine glucose tests. In addition, measurement of 1,5-anhydroglucitol (1,5-AG), a glucose analog that competes with glucose for renal reabsorption, is an unreliable method to assess glycemic control.

Adverse reactions reported in clinical studies were similar between placebo-control studies and placebo-controlled metformin add-on studies for canagliflozin. The most common adverse reactions associated with initiation of metformin therapy are mostly gastrointestinal in nature. Long-term use of metformin may lead to vitamin B12 deficiency, which may be reversed with discontinuation of metformin or vitamin B12 supplementation. Monitor serum vitamin B12 every two to three years.

SPECIAL POPULATIONS [38,39,40,41,42]

Pediatrics

The safety and efficacy of canagliflozin (Invokana), canagliflozin/metformin (Invokamet), dapagliflozin (Farxiga), dapagliflozin/metformin ER (Xigduo XR), and empagliflozin (Jardiance) have not been determined in patients under 18 years old.

Geriatrics

No dosage adjustment is recommended for canagliflozin, dapagliflozin, or empagliflozin based on age.

Patients 65 years and older may be at increased risk of experiencing intravascular volume-depletion adverse reactions and renal impairment compared to younger patients, while on SGLT2 inhibitor therapy; for canagliflozin, this may occur particularly with the 300 mg dose. Patients who were 75 years of age and older had more prominent increases in incidence. Studies with empagliflozin reported increased risk of urinary tract infections in those 75 years of age and older. When comparing younger patients to older patients, the older patients experienced smaller reductions in HbA_1C relative to placebo.

Although differences in responses between elderly and younger patients are not expected, controlled studies of metformin did not include sufficient numbers of elderly patients. Due to the age-related decline of renal function, initiation and maintenance dosing of metformin should be based on a conservative approach in patients with advanced age.

Pregnancy

Canagliflozin (Invokana), canagliflozin/metformin (Invokamet), dapagliflozin (Farxiga), dapagliflozin/metformin XR (Xigduo XR), and empagliflozin (Jardiance) are Pregnancy Category C.

Renal Impairment

Canagliflozin (Invokana), canagliflozin/metformin (Invokamet), dapagliflozin (Farxiga), and empagliflozin (Jardiance) are contraindicated in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] less than 30 mL/min/1.73 m^2), end stage renal disease (ESRD), and in patients on dialysis. These agents are not expected to be effective in these patient populations.

Patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) had less glycemic efficacy and higher occurrence of intravascular volume adverse reactions, renal-related adverse reactions, and decreases in eGFR with canagliflozin compared to patients with mild renal impairment or normal renal function. Increased potassium levels were more often experienced in patients taking 300 mg of canagliflozin.

Dapagliflozin is not recommended for use in patients with moderate renal insufficiency (eGFR 30 to less than 60 mL/min/1.73 m^2). Compared to placebo-treated patients, patients with moderate renal insufficiency did not have improved glycemic control and had more renal-related adverse effects and more bone fractures.

Dapagliflozin/metformin ER (Xigduo XR) should not be used in patients with moderate to severe renal impairment, defined as eGFR less than 60 mL/min/1.73 m^2 or CrCL less than 60 mL/min, or ESRD.

No dose adjustment of empagliflozin is needed if eGFR is at least 45 mL/min/1.73 m^2. However, clinical studies in patients with mild and moderate renal impairment reported a decreased glucose lowering benefit of empagliflozin 25 mg with decreasing level of renal function. This population also experienced an increase in incidence of adverse reactions related to volume depletion and urinary tract infection in patients with worsening renal function.

Hepatic Impairment

Canagliflozin (Invokana) is not recommended for use in patients with severe hepatic impairment. Dosage adjustments are recommended for those with moderate impairment, but not for patients with mild impairment. In general, canagliflozin/metformin (Invokamet) and dapagliflozin/metformin ER (Xigduo XR) are not recommended in patients with hepatic impairment due to increased risk of lactic acidosis.

No dose adjustment is recommended for dapagliflozin and empagliflozin for patients with hepatic impairment. However, the safety and efficacy of these agents have not been specifically studied in patients with severe hepatic impairment.

DOSAGES [43,44,45,46,47]

Drug	Parameters	Dosage	Availability
canagliflozin (Invokana)	Recommended starting dose	100 mg once a day taken before the first meal each day (once daily)	100, 300 mg tablet
	Patients tolerating canagliflozin 100 mg daily, requiring additional glycemic control, and have an eGFR of at least 60 mL/min/1.73 m^2	300 mg once daily	
	Moderate renal impairment (eGFR 45 to 59 mL/min/1.73m^2)	100 mg once daily	
canagliflozin / metformin (Invokamet)	Recommended starting dose in patients on metformin	For patients on metformin: Switch to Invokamet containing canagliflozin 50 mg with a similar total daily dose of metformin taken twice daily with meals For patients on canagliflozin: Switch to Invokamet containing metformin 500 mg with a similar total daily dose of canagliflozin taken twice daily with meals For patients on canagliflozin and metformin: Switch to Invokamet containing the same total daily doses of each component taken twice daily with meals	50/500, 50/1,000, 150/500, 150 mg/1,000 mg immediate-release capsule
	Moderate renal impairment (eGFR 45 to 59 mL/min/1.73m^2)	50 mg twice daily	
dapagliflozin (Farxiga)	Recommended starting dose	5 mg once daily, taken in the morning, with or without food	5, 10 mg tablet
	Patients tolerating dapagliflozin 5 mg once daily who require additional glycemic control	10 mg once daily	
dapagliflozin / metformin ER (Xigduo XR)	Recommended starting dose	Once daily, taken in the morning with food Gradually escalate dosage to reduce gastrointestinal side effects due to metformin Do not exceed 10 mg dapagliflozin/1000 mg metformin XR per day Swallow whole, do not crush, cut, or chew	5/500 mg, 500/1000 mg, 10/500 mg, 10/1,000 mg extended-release tablet
empagliflozin (Jardiance)	Recommended starting dose	10 mg once daily in the morning, with or without food.	10, 25 mg tablet
	Patients tolerating empagliflozin 10 mg once daily who require additional glycemic control	25 mg once daily	

Renal function should be assessed prior to starting SGLT-2 inhibitor therapy. Do not initiate canagliflozin or empagliflozin if eGFR is below 45 mL/min/1.73 m^2, dapagliflozin if eGFR is below 60 mL/min/1.73 m^2. Do not initiate canagliflozin/metformin (Invokana) in patients with serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females or eGFR is below 45 mL/min/1.73 m^2. Do not initiate dapagliflozin/metformin ER in patients with serum eGFR less than 60 mL/min/1.73 m^2 or CrCL less than 60 mL/min. Discontinue SGLT2 inhibitor therapy if eGFR persistently falls below these respective eGFR levels.

CLINICAL TRIALS

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all brand names in this class. Randomized, comparative, controlled trials performed in the United States comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Using these criteria, numerous studies were found. Data were further excluded based on the following characteristics: formulation or drug not available in U.S., single-blind or open-label design, or single-dose study. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Due to a paucity of double-blind, direct comparator trials, studies with a placebo comparator were included in the absence of comparative trials.

There have been no clinical efficacy studies conducted with the canagliflozin/metformin combination product Invokamet. Bioequivalence of the combination product to canagliflozin and metformin co-administered as individual tablets was demonstrated in healthy subjects.

canagliflozin (Invokana) monotherapy

A 26 week double-blind, placebo-controlled study was performed in 584 patients with type 2 diabetes who were not controlled by diet and exercise in order to determine the safety and efficacy of canagliflozin.[48,49] Patients who were taking other antihyperglycemics (n=281) discontinued the medication and entered an eight-week washout period followed by a two-week, single-blind, placebo run-in period. Patients who were not taking oral antihyperglycemics (n=303) were allowed to enter the two-week, single-blind, placebo run-in period immediately. After the placebo run-in period, patients were then randomized to receive canagliflozin 100 mg, canagliflozin 300 mg, or placebo once daily. Primary endpoint was the change from baseline in HbA1c. At week 26, HbA1c was significantly reduced from baseline with canagliflozin 100 and 300 mg compared with placebo (-0.77, -1.03 and 0.14 percent, respectively; p<0.001 for both). The percent of patients achieving an HbA1c of less than seven percent

was 45, 62, and 21 percent for patients treated with canagliflozin 100 mg, canagliflozin 300 mg, and placebo once daily, respectively (p<0.001). Canagliflozin 100 mg and 300 mg once daily also improved fasting plasma glucose (FPG) compared to placebo (-27, -35, and 8 mg/dL, respectively). Patients treated with canagliflozin 100 mg and 300 mg once daily also had greater reductions in the two-hour postprandial glucose (PPG) compared to placebo (-43, -59, and 5 mg/dL, respectively) and significant reductions in body weight compared to placebo (-2.8, -3.9, and -0.6 percent, respectively; p<0.001 for both). Statistically significant changes in systolic blood pressure were also observed for 100 mg and 300 mg dosages (-3.7 mmHg and -5.4 mmHg, respectively; p<0.001).

canagliflozin add-on therapy to metformin

A double-blind, placebo- and active-controlled study was performed in 1,284 patients with type 2 diabetes who were inadequately controlled on metformin monotherapy (greater than or equal to 2,000 mg/day, or at least 1,500 mg/day if higher dose not tolerated) to assess the safety and efficacy of canagliflozin when combined with metformin.[50,51] If patients were taking less than the required metformin dose or were taking metformin plus another antihyperglycemic (n=275), they were switched to metformin monotherapy for at least eight weeks before they were allowed to enter the two-week, single-blind, placebo run-in. Patients who were already taking the required metformin dose (n=1,009) were immediately allowed to enter a two-week, single-blind, placebo run-in period. After completing the placebo run-in phase, patients were randomized to receive canagliflozin 100 mg, canagliflozin 300 mg, sitagliptin 100 mg, or placebo once daily with metformin for 26 weeks (Period I). Patients who completed Period I then entered Period II for an additional 26 weeks during which those who were initially received placebo switched to sitagliptin 100 mg in a blinded fashion, while the other patients in the study continued their original study drug. Comparisons were performed for canagliflozin versus placebo at week 26 and canagliflozin versus sitagliptin at week 52. At week 26, the study indicated that the addition of canagliflozin 100 mg and 300 mg resulted in statistically significant improvements in HbA1C compared to placebo with metformin(−0.79, –0.94 and –0.17 percent, respectively; p<0.001 for both). The percent of patients achieving an HbA1C less than 7 percent was 58, 46, and 30 percent with the addition of canagliflozin 300 mg and 100 mg, and placebo, respectively. A larger reduction in FPG occurred with canagliflozin 100 mg (-27 mg/dL) and canagliflozin 300 mg (-38 mg/dL) compared to placebo (2 mg/dL). A reduction in PPG was also greater with canagliflozin 100 mg (-48 mg/dL) and canagliflozin 300 mg (-57 mg/dL) compared to placebo (-10 mg/dL). Patients treated with canagliflozin 100 mg and 300 mg once daily also had greater reductions in body weight compared to placebo (-3.7, -4.2 and -1.2 percent, respectively; p<0.001 for both). At week 52, canagliflozin 100 mg and 300 mg demonstrated non-inferiority, and canagliflozin 300 mg demonstrated statistical superiority, to sitagliptin in lowering HbA1c (−0.73%, –0.88%,–0.73%, respectively). Canagliflozin 100 mg and 300 mg reduced body weight compared to sitagliptin at week 52 (–3.8, –4.2 and –1.3 percent, respectively; p<0.001). Incidence of hypoglycemia was higher with canagliflozin; 6.8 percent with both canagliflozin doses compared to 4.1 percent with sitagliptin and 2.7 percent with placebo/sitagliptin at during 52 weeks. Statistically significant mean changes in systolic blood pressure relative to placebo were observed with canagliflozin 100 mg and 300 mg (-5.4 mmHg and -6.6 mmHg, respectively; p<0.001 for both doses).

The safety and efficacy of canagliflozin in combination with metformin were studied in 1,450 patients with type 2 diabetes who were inadequately controlled on metformin monotherapy (greater than or equal to 2,000 mg/day, or at least 1,500 mg/day, if higher dose not tolerated) in a 52-week, double-blind, active-controlled study.[52] After a two-week, single-blind, placebo run-in period, patients who

were already taking the maximum required metformin dose (n=928) were randomized. Other patients (n=522) were switched to metformin monotherapy for ten weeks and then entered the two week single-blind run-in period. After the two-week run-in period, patients were randomized to receive canagliflozin 100 mg or 300 mg, or glimepiride (titration up to 6 mg or 8 mg) given once daily with metformin. The study concluded that addition of canagliflozin 100 mg and glimepiride had similar reductions in HbA1C; only canagliflozin 300 mg plus metformin provided a greater reduction from baseline in the HbA1C level when compared to glimepiride plus metformin (95% CI). The percent of patients reaching an HbA1C of less than seven percent was 54, 60, and 56 percent for patients treated with canagliflozin 100 mg, canagliflozin 300 mg, and glimepiride, respectively. A larger reduction in FPG occurred in the canagliflozin 100 mg (-24 mg/dL) and canagliflozin 300 mg (-28 mg/dL) compared to glimepiride (-18 mg/dL). Patients in the canagliflozin 100 mg and 300 mg groups also had greater reductions in body weight compared to the glimepiride group (-4.2, -4.7, and +1.0 percent, respectively; p<0.001 for both).

canagliflozin add-on therapy to sulfonylurea

An 18-week, double-blind, placebo-controlled sub-study was performed in 127 patients with type 2 diabetes who were inadequately controlled on sulfonylurea monotherapy in order to assess the safety and efficacy of canagliflozin combined with sulfonylurea.[53] Patients taking sulfonylurea monotherapy and who were stable on a protocol specified dose (greater than or equal to 50 percent maximum dose) for at least ten weeks completed a two-week, single-blind, placebo run-in phase. Upon completion of the run-in phase, patients with poor glycemic control were randomized to add-on therapy with canagliflozin 100 mg, canagliflozin 300 mg, or placebo once daily. The study concluded that canagliflozin 100 mg and 300 mg daily resulted in statistically significant improvements in HbA1C compared to placebo when combined with a sulfonylurea (p<0.001). Canagliflozin 300 mg daily compared to placebo also resulted in higher rates of achieving an HbA1c of less than seven percent (33 versus 5 percent) and larger reductions in FPG (-36 versus +12 mg/dL).

canagliflozin add-on therapy to metformin and sulfonylurea

The efficacy and safety of canagliflozin in combination with metformin and a sulfonylurea were studied in 469 patients with type 2 diabetes who were inadequately controlled on combined metformin (greater than or equal to 2,000 mg/day, or at least 1,500 mg/day if higher dose not tolerated) and sulfonylurea (maximum or near maximum dose) therapy in a 26-week, double-blind, placebo-controlled study.[54] Patients who were on protocol-specified doses of metformin and sulfonylurea (n=372) were allowed to directly enter a two-week, single-blind, placebo run-in period. Other patients (n=97) were required to be on a stable protocol dose of metformin and sulfonylurea for eight weeks or more before entering the two-week run-in phase. After the run-in period, patients were randomized to receive canagliflozin 100 mg or 300 mg, or placebo taken once daily added to metformin and sulfonylurea. The study resulted in canagliflozin 100 mg and 300 mg having statistically significant improvements in HbA1C compared to placebo when combined with metformin and sulfonylurea (p<0.001). More patients treated with canagliflozin 100 mg or 300 mg obtained an HbA1c less than seven percent (43 percent and 57 percent, respectively) compared to placebo (18 percent) (p<0.001). Canagliflozin 100 mg and 300 mg lowered FPG (-18 mg/dL and -31 mg/dL, respectively) more than placebo (4 mg/dL). Patients in the canagliflozin 100 mg and 300 mg groups also had greater reductions in body weight compared to the placebo group (-2.1, -2.6, and -0.7 percent, respectively; p<0.001 for both).

A 52-week, double blind, active-controlled study enrolled 755 patients with type 2 diabetes who were uncontrolled on a combination of metformin (greater than or equal to 2,000 mg/day, or at least 1,500 mg/day, if higher dose not tolerated) and sulfonylurea (maximum or near maximum dose) was performed to compare the efficacy and safety of the addition of canagliflozin 300 mg versus sitagliptin 100 mg to metformin and sulfonylurea.[55,56] Patients already on the protocol-specified doses of metformin and sulfonylurea (n=716) were allowed to enter a two-week single-blind, placebo run-in phase. Other patients (n=39) had to be stabilized on the protocol-specified dose of metformin and sulfonylurea for at least eight weeks before entering the two-week run-in period. All patients were then randomized to canagliflozin 300 mg or sitagliptin 100 mg plus metformin and sulfonylurea. A total of 464 patients completed the 52-week treatment period. At the conclusion of the study, it was determined that canagliflozin 300 mg resulted in a greater HbA1C reduction compared to sitagliptin 100 mg when added to metformin and sulfonylurea ($p<0.05$). The rate of patients achieving an HbA1C of less than seven percent was higher in the canagliflozin 300 mg treatment group (48 percent) versus the sitagliptin 100 mg treatment group (35 percent). The addition of canagliflozin 300 mg also lowered FPG more than sitagliptin 100 mg (-30 and -6 mg/dL, respectively). Patients in the canagliflozin 300 mg group also had greater reductions in body weight compared to the sitagliptin group (-2.5 and -0.3 percent, respectively; $p<0.001$). A decrease in systolic blood pressure was seen with canagliflozin 300 mg, while a small increase was reported with sitagliptin 100 mg (-5.06 mmHg versus +0.85 mmHg).

canagliflozin add on therapy to metformin and pioglitazone

A 26-week, double-blind, placebo-controlled study was performed in 342 patients with type 2 diabetes who were poorly controlled on metformin (greater than or equal to 2,000 mg/day, or at least 1,500 mg/day, if higher dose not tolerated) and pioglitazone (30 or 45 mg/day) to evaluate the efficacy and safety of canagliflozin plus metformin and pioglitazone.[57] Patients (n=163) who were already on protocol-specific doses of metformin and pioglitazone entered a two-week, single-blind, placebo run-in period. Other patients (n=181) were required to be on metformin and pioglitazone at protocol-specific stable doses for at least eight weeks before entering the two-week run-in period. After the run-in phase, patients were then randomized to canagliflozin 100 mg or 300 mg, or placebo given once daily with metformin and pioglitazone. The study resulted in the addition of canagliflozin 100 mg and 300 mg having statistically significant improvements in HbA1C compared to placebo ($p<0.001$). Canagliflozin 100 mg and 300 mg resulted in a greater percentage of patients achieving an HbA1c level of less than seven percent compared to placebo (47, 64, and 33 percent, respectively) ($p<0.001$). Canagliflozin 100 mg and 300 mg had larger reductions in FPG (-27 and -33 mg/dL, respectively) compared to placebo (3 mg/dL). Patients in the canagliflozin 100 mg and 300 mg groups also had greater reductions in body weight compared to placebo when add to metformin and pioglitazone (-2.8, -3.8 and -0.1 percent, respectively; $p<0.001$). In addition, statistically significant mean changes from baseline in systolic blood pressure relative to placebo were -4.1 mmHg and -3.5 mmHg with canagliflozin 100 mg and 300 mg, respectively ($p<0.05$ for both doses).

canagliflozin add on therapy to insulin

An 18-week, double-blind, placebo-controlled substudy of a cardiovascular study was performed to assess the efficacy and safety of canagliflozin in combination with insulin.[58] The study included 1,718 patients with type 2 diabetes who were uncontrolled on insulin at doses of at least 30 units/day or who were on insulin in combination with other antihyperglycemic agents. Patients entered a two-week, single-blind, placebo run-in period after at least ten weeks of basal, bolus, or basal/bolus insulin

therapy. After the run-in period, patients were randomized to receive canagliflozin 100 mg or 300 mg, or placebo once daily plus insulin. The study concluded that canagliflozin-treated patients experienced a statistically significant improvement in their HbA_1C levels ($p<0.001$) compared to placebo treated patients when added to insulin. The percent of patients' achieving an HbA1c of less than seven percent was 20, 25, and 8 percent for canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively. Canagliflozin 100 mg and 300 mg also resulted in a larger decrease in FPG (-19 and -25 mg/dL, respectively) compared to placebo (4 mg/dL). Patients in the canagliflozin 100 mg and 300 mg groups also had greater reductions in body weight compared to the placebo group (-1.8, -2.8, and -0.1 percent, respectively; $p<0.001$). Statistically significant mean change in systolic blood pressure relative to placebo was reported with both doses of canagliflozin; -3.5 mmHg for the 100 mg dose ($p=0.023$) and -6 mmHg for the 300 mg dose ($p<0.001$).

dapagliflozin (Farxiga) monotherapy

Dapagliflozin was studied as monotherapy in treatment-naïve patients with type 2 diabetes. A 24-week randomized, double-blind, placebo-controlled phase 3 trial (n=485) randomly assigned patients to one of seven arms to receive once-daily placebo or dapagliflozin 2.5 mg, 5 mg, or 10 mg once daily in the morning (main cohort) or evening (exploratory cohort).[59] The primary endpoint was change in baseline from HbA1c in the main cohort. At 24 weeks, the adjusted mean HbA1c reductions from baseline were -0.58 for dapagliflozin 2.5 mg, -0.77 for dapagliflozin 5 mg, and -0.89 for dapagliflozin 10 mg compared to -0.2 for placebo. These reductions were statistically significant with 5 mg and 10 mg dapagliflozin ($p=0.0005$ and $p<0.0001$, respectively). An increased incidence in signs and symptoms and other reports suggestive of urinary tract infections (UTIs) and genital infections were noted with dapagliflozin treatment.

dapagliflozin initial combination therapy with metformin extended-release (Xigduo XR)

A total of 1,241 treatment-naïve patients with inadequately controlled type 2 diabetes (HbA1c >7.5 % and <12%) participated in two active-controlled studies of 24-week duration to evaluate the safety and efficacy of initial therapy with dapagliflozin, metformin extended-release, or the combination.[60] Patients were randomized in a double-blind fashion to one of three treatment arms: a combination of dapagliflozin and metformin ER or monotherapy with either dapagliflozin or metformin ER. In the first trial, dapagliflozin was dosed at 5 mg daily and, in the second trial, dapagliflozin was dosed at 10 mg daily. Metformin ER in combination and as monotherapy was titrated to 2,000 mg per day. The primary endpoint was HbA1c change from baseline; secondary endpoints included change in fasting plasma glucose (FPG) and weight. In both trials, combination therapy led to significantly greater reductions in HbA1c compared with either monotherapy. In Study-1 HbA1c reductions were -2.05 for dapagliflozin plus metformin ER, -1.19 for dapagliflozin, and -1.35 for metformin ER ($p<0.0001$). In study two, HbA1c reductions were -1.98 for dapagliflozin + metformin ER, -1.45 for dapagliflozin, and -1.44 for metformin ER ($p<0.0001$). Single agent dapagliflozin 10 mg was non-inferior to single agent metformin ER for reducing HgA1c in this study. Combination therapy was also statistically superior to monotherapy with either agent in reduction of FPG ($p<0.0001$ for both studies); combination therapy was more effective than metformin ER for weight reduction ($p<0.0001$). Events suggestive of genital infection were reported in 6.7 percent, 6.9 percent, and two percent (Study one) and 8.5 percent, 12.8 percent, and 2.4 percent (Study two) of patients in combination, dapagliflozin, and metformin ER groups,

respectively; events suggestive of UTIs were reported in 7.7 percent, 7.9 percent, and 7.5 percent (Study one) and 7.6 percent, 11 percent, and 4.3 percent (Study two) of patients, respectively.

dapagliflozin versus placebo as add-on to metformin

Patients with inadequate glycemic control (HbA1c ≥7% and ≤ 10%) receiving a dose of at least 1,500 mg/day of metformin (n=546) were randomized to add-on either dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo for 24 weeks.[61] Patients receiving dapagliflozin 5 mg or 10 mg achieved statistically significant improvements in HbA1c and FPG, as well as statistically significant reduction in body weight compared with placebo at week 24 ($p<0.0001$ for all three parameters versus placebo plus metformin)

dapagliflozin versus glipizide as add-on to metformin

A 52-week, double-blind, multicenter, active-controlled, noninferiority trial randomized patients receiving metformin monotherapy (minimum dose 1,500 mg/day) and inadequate glycemic control (HbA1c ≥ 6.5% and ≤ 10%) to add-on dapagliflozin or glipizide.[62] Initial doses were dapagliflozin 2.5 mg or glipizide 5 mg. Glipizide and dapagliflozin were up-titrated over 18 weeks to optimal glycemic effect (FPG < 110 mg/dL) or to the highest dose level (up to a maximum of 20 mg of glipizide or 10 mg of dapagliflozin) as tolerated by the patients. At the end of the titration period, 87 percent of patients with dapagliflozin had been titrated to the maximum study dose (10 mg) while only 73 percent of glipizide patients were receiving the maximum dose (20 mg). The primary endpoint, adjusted mean HbA1c reduction with dapagliflozin compared with glipizide, was statistically non-inferior at 52 weeks. Secondary endpoints included adjusted mean weight loss and proportion of patients experiencing hypoglycemia. Dapagliflozin produced significant adjusted mean weight loss (-3.2 kg) versus weight gain (1.2 kg) with glipizide ($p<0.001$). The proportion of patients experiencing hypoglycemia was 3.4 percent for dapagliflozin and 39.7 percent for glipizide ($p<0.001$).

dapagliflozin add-on to a sulfonylurea

A 24-week placebo-controlled study evaluated dapagliflozin when added-on to glimepiride monotherapy (minimum dose 4 mg) in patients with inadequate glycemic control (HbA1c ≥ 7% and ≤ 10%).[63] Patients (n= 597) were randomized to dapagliflozin 5mg, 10 mg, or placebo, in addition to glimepiride 4 mg per day. In combination with glimepiride, dapagliflozin 10 mg provided statistically significant improvement in HbA1c, FPG, 2-hour post prandial glucose (PPG), and statistically significant reduction in body weight compared with placebo plus glimepiride at week 24.

dapagliflozin add-on to a thiazolidinedione

Patients (n=420) on a stable dose of pioglitazone (either 30 mg or 45 mg per day) who had inadequate glycemic control (HbA1c ≥ 7% and ≤ 10.5%) for 12 weeks were randomized to dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo, in addition to their current dose of pioglitazone.[64] In combination with pioglitazone, treatment with dapagliflozin 10 mg provided statistically significant improvements in HbA1c, 2-hour PPG, FPG, the proportion of patients achieving HbA1c < 7%, and a statistically significant reduction in body weight compared with placebo plus pioglitazone.

dapagliflozin add-on to a DPP-4 Inhibitor with or without metformin

A total of 452 patients who were either drug naïve or who were treated at baseline with metformin or a dipeptidyl peptidase 4 (DPP-4) inhibitor alone or in combination and who had inadequate glycemic control (HbA1c ≥7% and ≤10%) participated in a 24-week placebo-controlled study to evaluate dapagliflozin in combination with the DPP-4 inhibitor, sitagliptin, with or without metformin.[65] Patients were stratified based on the presence or absence of background metformin (minimum 1,500 mg per day) and, within each stratum, were randomized to dapagliflozin 10 mg plus sitagliptin 100 mg once daily or placebo plus sitagliptin 100 mg once daily. Prior to randomization, 37 percent of patients were drug naïve, 32 percent were on metformin alone, 13 percent were on a DPP4 inhibitor alone, and 18 percent were on a DPP4 inhibitor plus metformin. In combination with sitagliptin (with or without metformin), dapagliflozin provided statistically significant improvements in HbA1c, FPG, and a statistically significant reduction in body weight compared with placebo plus sitagliptin (with or without metformin) at 24 weeks.

dapagliflozin add-on combination therapy with insulin

A double-blind, placebo-controlled, multicenter trial randomized a total of 71 patients to placebo, dapagliflozin 10 mg or dapagliflozin 20 mg in patients who were on a stable dose regimen of insulin and at least one oral antidiabetic agent, such as a metformin with or without a thiazolidinedione.[66] Upon initiation of dapagliflozin, patients were changed to an open-label therapy with 50 percent of their usual daily insulin dose. Both doses of dapagliflozin decreased HbA1c, FPG, and PPG compared to placebo and overall adverse events were balanced across all groups.

A 24-week, placebo-controlled, multicenter study examined 808 patients with inadequate glycemic control (HbA1c between 7.5% and 10.5%) who were on a stable insulin regimen (mean dose of at least 30 IU per day) and a maximum of two oral antidiabetic medications, including metformin.[67] After the initial 24 weeks, a 24-week extension was allowed, as well as an additional 56-week extension period for a total of 104 weeks. In this study, 50 percent of patients were on insulin monotherapy and 50 percent were on one or two oral antidiabetic agents in addition to insulin. Patients were randomized to dapagliflozin 2.5 mg, dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo and stratified according to the presence or absence of background oral antidiabetic agents. The primary endpoint was change in HbA1c from baseline after 24 weeks. Secondary outcomes included changes in body weight, insulin dose, and FPG at 24 weeks. No dose modifications of study medication or other oral antidiabetic medications were allowed during the treatment phase except to decrease the dose of oral antidiabetic medications if hypoglycemia became a concern in patients who had already discontinued insulin. Insulin was down-titrated if two or more self-monitored blood glucose readings were 80 mg/dL or less in the first seven days or less than 70 mg/dL after the first seven days. At week 24, all doses of dapagliflozin once daily resulted in a statistically significant reduction in HbA1 c levels compared to placebo. These differences were maintained at 48 weeks. The effect of dapagliflozin on HbA1c was similar in patients treated with insulin alone and patients treated with insulin plus oral antidiabetic agents. Significantly greater decreases in body weight occurred in all the dapagliflozin groups compared to placebo ($p<0.001$) and these differences were maintained at 48 weeks, as well. Mean daily insulin doses were decreased in all dapagliflozin groups compared to placebo at both 24 and 48 weeks ($p<0.001$). Higher incidences of urinary tract infections, genital infections, and hypoglycemic events were observed in the dapagliflozin groups compared to placebo. At week 104, 513 patients (63.6 percent) completed the study. Mean HbA1c changes from baseline at 104 weeks were -0.4

percent in the placebo group and -0.6 to -0.8 percent in the dapagliflozin groups.[68] In the placebo group, mean insulin dose increased by 18.3 IU/day and weight increased by 1.8 kg at 104 weeks, whereas in the dapagliflozin groups, insulin dose was stable and weight decreased by 0.9-1.4kg. Adverse events, including hypoglycemia, were similar between all groups. Proportions of patients with events suggestive of genital infection and of urinary tract infection (UTI) were higher with dapagliflozin versus placebo (genital infection 7.4-14.3 percent versus three percent; UTI 8.4-13.8 percent versus 5.6 percent) but most occurred in the first 24 weeks and most were single episodes that responded to routine management.

dapagliflozin as add-on to usual therapy

A randomized, double-blind, 24-week clinical trial with a 28-week extension was performed to assess the efficacy of dapagliflozin in 964 patients with type 2 diabetes mellitus and documented cardiovascular disease (CVD).[69,70] The study was stratified by age (<65 and ≥ 65). Patients were randomized to dapagliflozin 10 mg or placebo once daily added to their usual care. Total daily insulin doses were reduced by 25 percent at the start of the study. Primary endpoints were change from baseline in HbA1c and proportion of participants achieving a three-item endpoint of reduction HbA1c ≥ 0.5%, decrease in body weight of at least three percent, and reduction of systolic blood pressure ≥ 3 mmHg at 24 weeks. Forty-seven percent were aged 65 years and older and 7.7 percent were 75 years and older, mean duration of type 2 diabetes mellitus was 13 years, mean baseline HbA1c was 8.1%, and approximately 60 percent of patients on insulin therapy. The placebo-corrected change in HbA1c with dapagliflozin was -0.4% at Week-24. The difference in adjusted mean change in body weight was -2.07 kg ($p<0.0001$) and the difference in change in mean seated systolic blood pressure was -3.76 mmHg ($p=0.025$). Significantly more participants achieved the three-item endpoint with dapagliflozin than with placebo (10 versus 1.9 percent, respectively). Similar results were reported in both groups. Hypoglycemia was reported in 28.2 percent of patients who received dapagliflozin compared to 25.3 percent who received placebo.

empagliflozin (Jardiance) monotherapy

A randomized, double-blind, placebo-controlled, parallel group study evaluated the efficacy and safety of empagliflozin monotherapy in 986 treatment-naïve adults with type 2 diabetes who were inadequately controlled with diet and exercise.[71,72,73] After a two-week open-label placebo run-in phase, 986 patients who remained inadequately controlled and had an HbA1c between 7% and 10% were randomized to 24 weeks of daily oral empagliflozin 10 mg or 25 mg, placebo, or sitagliptin 100 mg as a comparator. Patients with HbA1c > 10% in the open-label phase received empagliflozin 25 mg. Primary endpoint was the change in HbA1c from baseline. At Week 24, treatment with empagliflozin 10 mg and 25 mg and sitagliptin provided statistically significant reductions in HbA1c compared to placebo (-0.74, -0.85, -0.73, respectively; $p <0.0001$ for all). Significant reductions were also reported with secondary endpoints of fasting plasma glucose (FPG). Patients on empagliflozin (-1.93 kg for 10 mg, -2.15 kg for 25 mg, $p<0.001$ for both) experienced significantly greater weight loss than those assigned to sitagliptin (+0.52 kg) and placebo. The incidence of reported hypoglycemic events was low in all groups, and was of mild intensity. Changes in eGFR were small and were similar across all groups. At Week 24, the placebo-adjusted reduction in systolic blood pressure was statistically significant for empagliflozin 10mg (-2.6 mmHg; $p=0.0231$) and empagliflozin 25 mg (-3.4 mmHg; $p=0.0028$).

empagliflozin add-on to metformin

In a double-blind, placebo-controlled trial, a total of 637 patients with type 2 diabetes who were inadequately controlled on metformin (≥ 1,500 mg/day or maximum tolerated dose) were randomized to add-on therapy with empagliflozin 10 mg or 25 mg daily or placebo.[74] At Week 24, add-on treatment with either dose of empagliflozin resulted in statistically significant reductions compared to placebo in HbA1c (-0.7, -0.8, and -0.1 percent, respectively p<0.0001), FPG (-20, -22, and +6 mg/dL), and body weight (-2.5, -2.9, and -0.5 percent; respectively). In addition, treatment with empagliflozin led to a significant reduction in systolic blood pressure compared to placebo (placebo-corrected -4.1 mmHg for empagliflozin 10 mg and -4.8 mmHg for empagliflozin 25 mg; p<0.0001 for both strengths).

empagliflozin plus metformin versus glimepiride plus metformin

In a double-blind study, 1,545 patients with inadequately controlled type 2 diabetes with metformin (≥ 1,500 mg/day or maximum tolerated dose) were randomized to add-on with empagliflozin 25 mg daily or glimepiride 1-4 mg daily.[75,76] At 52 weeks, empagliflozin 25 mg and glimepiride produced similar reductions in HbA1c. Each agent resulted in reductions in FPG (-19 and -9 mg/dL, respectively). Reported changes in body weight were -3.9 percent for empagliflozin and +2 percent for glimepiride. The mean daily dose of glimepiride was 2.7 mg (maximal approved dose in the U.S. is 8 mg/day). There was a significant difference in the adjusted mean change in systolic blood pressure between the two groups (-3.6 mmHg for empagliflozin versus 2.2 mmHg for glimepiride; p<0.0001). In addition, at 104 weeks, empagliflozin was shown to be non-inferior to glimepiride.[77] The incidence of adverse reactions, including serious reactions, was similar between treatment groups.

empagliflozin add-on to metformin and sulfonylurea

In a 24-week double-blind, placebo-controlled study, 666 patients with type 2 diabetes who were inadequately controlled (HbA1c 7-10%) on metformin (≥ 1,500 mg/day or maximum tolerated dose) plus a sulfonylurea (at least half the recommended dose or maximum tolerated dose) were randomized to receive add-on therapy with empagliflozin 10 mg or 25 mg daily, or placebo.[78,79] Treatment with either dose of empagliflozin provided statistically significant reductions compared with placebo in HbA1c (-0.8, -0.8, and -0.2 percent; respectively; p<0.0001 for both), FPG (-23, -23, and +6 mg/dL, respectively), and body weight (-2.9, -3.2, and -0.5 percent, respectively).

empagliflozin add-on to pioglitazone with or without metformin

In a 24-week double-blind, placebo-controlled study, patients with type 2 diabetes inadequately controlled on metformin (≥ 1,500 mg/day) and pioglitazone (≥30 mg/day) entered an open-label two week placebo run-in phase.[80,81] After which, 498 patients with inadequate glycemic control (HbA1c 7-10%) were randomized to daily empagliflozin 10 mg or 25 mg or placebo, in combination with pioglitazone, with or without metformin. Of the patients treated, 75.5 percent were on background therapy with pioglitazone plus metformin, while the remaining 24.5 percent were on background pioglitazone alone. Both doses of empagliflozin compared with placebo resulted in statistically significant reductions in HbA1c (-0.6, -0.7, and -0.1 percent, respectively; p<0.0001), FPG (-17, -22, and +7 mg/dL, respectively), and body weight (-2, -1.8, and -0.6 percent, respectively). Empagliflozin reduced HbA1c in patients on background pioglitazone plus metformin and pioglitazone alone. Adverse events experienced were mild or moderate in intensity. A 52-week extension trial is also underway.

empagliflozin add-on to insulin with or without metformin and/or sulfonylureas

A 78-week double-blind, placebo-controlled study included 494 patients with type 2 diabetes inadequately controlled on insulin, with or without oral agents, to evaluate the efficacy of empagliflozin as add-on therapy to insulin.[82] Patients entered a two-week placebo run-in period on basal insulin (e.g., insulin glargine, insulin detemir, or NPH insulin) with or without metformin and/or sulfonylurea background therapy. Patients with inadequate glycemic control were then randomized to the addition of empagliflozin 10 mg or 25 mg, or placebo. Patients were maintained on a stable dose of insulin during the run-in period, and during the first 18 weeks of treatment. For the remaining 60 weeks, insulin could be adjusted. The mean total daily insulin dose at baseline for empagliflozin 10 mg, 25 mg, and placebo was 45 IU, 48 IU, and 48 IU, respectively. Empagliflozin in combination with insulin, with or without metformin and/or sulfonylurea, resulted in statistically significant reductions in HbA1c and FPG and body weight compared to placebo.

SUMMARY

According to the 2015 American Diabetes Association (ADA) Standards of Medical Care in Diabetes, the selection of medications should be patient-centric and prescribers should consider potential issues such as efficacy, cost, side effects, comorbidities, hypoglycemic risk, and patient preferences. If no contraindication exists and if well tolerated, metformin is the preferred initial treatment for type 2 diabetes. If monotherapy at the maximum tolerated dose does not achieve or maintain the desired HbA_1c level over three months, either a TZD, sulfonylurea, DPP-4 inhibitor, SGLT-2 inhibitor, GLP-1 receptor agonist, or insulin should be added. If target HbA1c is still not achieved after an additional three months, then an agent from a different group listed should be added.

The 2013 American Association of Clinical Endocrinologists (AACE) guidelines suggest SGLT2 inhibitors as a fifth, fourth, and third choice in monotherapy, dual therapy, and triple therapy, respectively, for glycemic control. The guidelines advise using SGLT2 inhibitors with caution and acknowledge that their place in therapy for diabetes management remains undefined due to lack of experience with these agents. The SGLT2 drugs will likely be used as add-on therapy to two or three other agents, including insulin, in patients who would benefit from weight loss.

While SGLT2 inhibitors are efficacious agents in reducing HbA1c, postprandial glucose, and fasting plasma glucose, as well as reducing systolic blood pressure and weight, the long-term safety of these agents remains to be established.

Available SGLT2 inhibitors include canagliflozin (Invokana), dapagliflozin (Farxiga), and empagliflozin (Jardiance). Two products are available that combine an SGLT2 inhibitor with metformin, canagliflozin/metformin (Invokana) and dapagliflozin/metformin ER (Xigduo XR).

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